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Abstract: BACKGROUND During times of organ scarcity and extended use of liver grafts, protective strategies in transplantation are gaining importance. We demonstrated in the past that volatile anesthetics such as sevoflurane attenuate ischemia-reperfusion injury during liver resection. In this randomized study, we examined if volatile anesthetics have an effect on acute graft injury and clinical outcomes after liver transplantation. METHODS Cadaveric liver transplant recipients were enrolled from January 2009 to September 2012 at 3 University Centers (Zurich/Sao Paulo/Ghent). Recipients were randomly assigned to propofol (control group) or sevoflurane anesthesia. Postoperative peak of aspartate transaminase was defined as primary endpoint, secondary endpoints were early allograft dysfunction, in-hospital complications, intensive care unit, and hospital stay. RESULTS Ninety-eight recipients were randomized to propofol (n = 48) or sevoflurane (n = 50). Median peak aspartate transaminase after transplantation was 925 (interquartile range, 512-3274) in the propofol and 1097 (interquartile range, 540-2633) in the sevoflurane group. In the propofol arm, 11 patients (23%) experienced early allograft dysfunction, 7 (14%) in the sevoflurane one (odds ratio, 0.64 (0.20 to 2.02, P = 0.45). There were 4 mortalities (8.3%) in the propofol and 2 (4.0%) in the sevoflurane group. Overall and major complication rates were not different. An effect on clinical outcomes was observed favoring the sevoflurane group (less severe complications), but without significance. CONCLUSIONS This first multicenter trial comparing propofol with sevoflurane anesthesia in liver transplantation shows no difference in biochemical markers of acute organ injury and clinical outcomes between the 2 regimens. Sevoflurane has no significant added beneficial effect on ischemia-reperfusion injury compared to propofol.

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Conditioning With Sevoflurane in Liver Transplantation: Results of a Multicenter Randomized Controlled Trial

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Background. During times of organ scarcity and extended use of liver grafts, protective strategies in transplantation are gaining importance. We demonstrated in the past that volatile anesthetics such as sevoflurane attenuate ischemia-reperfusion injury during liver resection. In this randomized study, we examined if volatile anesthetics have an effect on acute graft injury and clinical outcomes after liver transplantation. **Methods.** Cadaveric liver transplant recipients were enrolled from January 2009 to September 2012 at 3 University Centers (Zurich/Sao Paulo/Ghent). Recipients were randomly assigned to propofol (control group) or sevoflurane anesthesia. Postoperative peak of aspartate transaminase was defined as primary endpoint, secondary endpoints were early allograft dysfunction, in-hospital complications, intensive care unit, and hospital stay. **Results.** Ninety-eight recipients were randomized to propofol ($n = 48$) or sevoflurane ($n = 50$). Median peak aspartate transaminase after transplantation was 925 (interquartile range, 512–3274) in the propofol and 1097 (interquartile range, 540–2633) in the sevoflurane group. In the propofol arm, 11 patients (23%) experienced early allograft dysfunction, 7 (14%) in the sevoflurane one (odds ratio, 0.64 (0.20 to 2.02, $P = 0.45$)). There were 4 mortalities (8.3%) in the propofol and 2 (4.0%) in the sevoflurane group. Overall and major complication rates were not different. An effect on clinical outcomes was observed favoring the sevoflurane group (less severe complications), but without significance. **Conclusions.** This first multicenter trial comparing propofol with sevoflurane anesthesia in liver transplantation shows no difference in biochemical markers of acute organ injury and clinical outcomes between the 2 regimens. Sevoflurane has no significant added beneficial effect on ischemia-reperfusion injury compared to propofol.

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Liver transplantation is a well-established treatment option for end-stage liver disease and acute liver failure.

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Modification of surgical techniques, immunosuppressive regimen, and preservation solutions, as well as a better understanding of the use of marginal donors and recipients have

Study registered at ClinicalTrials.gov NCT00913276.

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B.B.S., J.M.B. were involved in study design, enrolment and follow-up of patients, data collection, writing of the report and manuscript writing. E.S. was involved in data collection and analysis and writing of the manuscript. P.D. and C.O. were involved in data collection and analysis. M.L. was involved in study design and manuscript writing. M.L.O. was involved in enrolment and follow-up of patients. E.R.F., J.R.F., J.O.A., and L.A.D. were involved in study design, enrolment and follow-up of patients and data collection. K.R., P.W., X.R., and L.D. were involved in study design, enrolment, and follow-up of patients and data collection. M.G. was involved in study design, enrolment and follow-up of patients and data collection. A.W. was involved in study design, data collection and analysis (liver histology). M.A.P. was involved in study design, statistical analysis and writing of the report. P.A.C. was involved in study design, enrolment, follow-up of patients and manuscript writing. S.B. was involved in study design, enrolment and follow-up of patients, data collection, writing of the report and manuscript writing.

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led to improved short- and long-term survivals.¹⁻⁷ It is well known that severity of hepatic ischemia-reperfusion injury also determines postoperative organ function and long-term graft survival.^{8,9}

Numerous strategies to protect livers from ischemia-reperfusion injury have been proposed, but only very few found their way into clinical practice. Anesthesiological protocols for liver transplantation differ between centers and guidelines exist; however, level 1 evidence is rare. Recently, the effect of volatile anesthetics, such as sevoflurane or desflurane, versus intravenous anesthesia using propofol was found to mitigate ischemia-reperfusion injury during liver resections in randomized studies.¹⁰⁻¹³ The cytoprotective effect of volatile anesthetics may either be initiated before the onset of ischemic injury (preconditioning), immediately on reperfusion (postconditioning), or for the entire surgical procedure (conditioning). Both preconditioning and postconditioning with volatile anesthetics reduced liver cell injury and complications after liver resection in our center.^{11,13} Other groups have corroborated these findings, such as Balzan et al.¹⁴ We therefore asked, if the use of volatile anesthetics might have an impact on outcomes after liver transplantation, which undoubtedly represents one of the most complex forms of ischemia-reperfusion injury to the liver.

This multicenter randomized clinical trial has a superiority trial design to prove that sevoflurane is better than propofol anesthesia in liver transplant recipients. We hypothesized that sevoflurane attenuates ischemia-reperfusion injury, measured by postoperative peak value of aspartate transaminase (AST) as primary endpoint, and also decreases the number of postoperative complications, defined as secondary endpoint.

METHODS

Study Design

This multicenter randomized controlled trial (RCT) was conducted in 3 well-established liver transplant centers: the University Hospital Zurich, Zurich, Switzerland, the Hospital das Clinicas, University of Sao Paulo School of Medicine, Sao Paulo, Brazil, and the Ghent University Hospital, Ghent, Belgium.

Patients enrolled in the study were randomly assigned to liver transplantation with either the intravenous anesthetic propofol (control group) or the volatile anesthetic sevoflurane (conditioning group). The aim of the trial was to test the hypothesis that conditioning with sevoflurane leads to better clinical outcomes as compared to the control group. This trial was approved by the institutional boards for human studies of the 3 centers (principal investigator and sponsor located at the University Hospital Zurich, protocol Nr. StV 15-2008; Swissmedic notification 2008DR4348), registered at ClinicalTrials.gov NCT00913276, and is reported according to the CONSORT statement.¹⁵

Study Population

Patients were assessed for eligibility between January 2009 and September 2012. Eligible participants were all adults (≥ 18 years) admitted for liver transplantation, who spoke the local language of the referred center and were able to provide written informed consent. Exclusion criteria were known or suspected allergy to propofol, soy, or egg, cardiovascular instability with norepinephrine infusion above

15 μg per minute before induction of anesthesia and severe impairment of renal and/or pulmonary function (e.g., dialysis, hemofiltration, $\text{FiO}_2 > 0.5$) before liver transplantation. Patients already included in another study were also excluded. Patients receiving organs from living donors as well as patients undergoing partial organ transplantation were not included.

Anesthesia

Anesthesia was performed in all 3 centers by a group of dedicated transplantation anesthesiologists. To maintain an optimal hemodynamic, patients were monitored with Swan-Ganz as well as with arterial and central venous catheters following respective departmental guidelines in each center.

Anesthesia was induced in both groups identically as follows: suppression of laryngoscopic stress response was achieved with intravenous application of fentanyl 3 $\mu\text{g}/\text{kg}$ or the initiation of remifentanyl infusion. Hypnosis was started with target control infusion of propofol set to effect site concentrations between 3 and 6 $\mu\text{g}/\text{mL}$, using programmable perfusors and the Schnider data set algorithm (Alaris PK, Cardinal Health, Dublin OH). Atracurium 0.5 mg/kg was applied to facilitate endotracheal intubation. In the setting of a rapid sequence induction, higher targets of propofol (5-7 $\mu\text{g}/\text{mL}$) and rocuronium (0.9 mg/kg) were chosen.

In the propofol group (control), anesthesia was maintained using propofol target control infusion as described above to obtain bispectral index values between 40 and 60 throughout the whole procedure (Covidien, Mansfield, MA). This method is used to monitor depth of anesthesia, measuring the effects of anesthetics and sedatives on the brain, which is based on an algorithmic analysis of the patient's electroencephalogram. Analgesia was achieved by applying boluses of fentanyl 1 to 2 $\mu\text{g}/\text{kg}$ and/or continuous infusion of remifentanyl up to 20 $\mu\text{g}/\text{kg}/\text{h}$ according to the need of the patient. Muscle relaxation was monitored with train of four stimulation of the left ulnar nerve. When train of four response was 2 or more, atracurium 5-10 mg was applied. In the sevoflurane group, however, propofol infusion was stopped immediately after induction and replaced by sevoflurane 0.6 to 1.5 minimum alveolar concentration supplemented with fentanyl, remifentanyl, and atracurium as described for the propofol group targeting the same bispectral index values. Therefore, according to a common definition established for cardiac surgery,^{16,17} the recipient experienced a conditioning with sevoflurane through the entire procedure, the transplanted liver itself a postconditioning. All patients were routinely admitted to the intensive care unit (ICU) intubated, and no immediate extubation was performed at the end of surgery. For the conditioning group, after termination of the surgical procedure, sevoflurane application was stopped, and propofol infusion reinstalled to maintain sedation for the transfer to the ICU.

Surgery

Deceased donor liver transplantation was performed by dedicated teams of liver transplantation surgeons using commonly used preservation fluids for organ procurement including UW, HDK, and Celsior. The operative procedure was performed using both caval replacement and Piggyback technique. Reperfusion of the liver started with opening of the portal vein, followed by opening of the artery. After arterial reperfusion, the bile duct was connected either to

the recipients' bile duct (choledocho-choledochostomy) or to a small-bowel loop (hepatico-jejunostomy). A back table biopsy of the donor liver was performed before implantation.

Outcomes

The primary endpoint was the peak value of AST after transplantation up to day 7, representing a frequently used marker for ischemia-reperfusion injury.^{13,18,19} Secondary endpoints included postoperative peak alanine transaminase (ALT), early allograft dysfunction (EAD), postoperative complications assessed according to the Clavien-Dindo complication score,²⁰ and duration of ICU and hospital stay.

Data Collection

A standardized data sheet was used in all 3 centers to collect the data of donors and recipients. The recipient-specific physical status was assessed according to the American Society of Anesthesiologists classification, the severity of liver disease based on the model for end-stage liver disease (MELD), international normalized ratio (INR), total bilirubin, and creatinine on admission.²¹ Expected liver weight was calculated using the formula of Urata et al²² and Lemke et al²³ to elucidate the possible mismatch between actual and expected graft weight. Cold ischemia time was defined as the time between aortic cross clamping in the donor until removal of the liver from ice, warm ischemia time as the time of removal from ice until portal vein reperfusion.

Liver-specific biochemical variables, such as AST, ALT, total bilirubin, alkaline phosphatase activity, and prothrombin time (Quick; INR) were recorded at standard timepoints: preoperatively (for donor and recipient) as well as postoperatively after 6 hours, on days 1, 3, 5, and 7. A validated definition of EAD was used: Quick value $\leq 41\%$ (INR ≥ 1.6), and/or ALT >2000 U/I and/or bilirubin ≥ 171 $\mu\text{mol/l}$ (≥ 10 mg/dl) at day 7 after liver transplantation.^{24,25} Complications were assessed during hospitalization, using the Clavien-Dindo classification with grade 0 (no complication) to grade V (death).²⁰ Complications grade IIIb or higher were defined as "major complications" because they require management under general anesthesia.

Donor liver histology was evaluated routinely, but particularly for the occurrence of macrosteatosis ($<$ or $\geq 30\%$) on frozen or formalin-fixed, paraffin-embedded biopsies stained with hematoxylin-eosin.¹³

Postoperative data and outcome were collected by coinvestigators in all 3 centers, blinded for the treatment of the patients.

Sample Size

We used previous trial data on transaminase levels after liver transplantation to estimate the mean postoperative peak AST level (primary outcome) without conditioning (mean of 1000 U/L) and its variability (standard deviation 300 U/L).²⁶ A sample size of 48 patients in each group showed a difference of 20% (or 200 U/L, respectively) in mean postoperative peak AST levels between the groups of normal and steatotic livers. We assumed a standard deviation of 300 U/L and chose a power of 90% at a significance level of 5% (2-sided). We defined these values as clinically relevant based on previous results in liver protection.²⁷ With an expected dropout rate of 10% (e.g., patients randomized but not undergoing liver transplantation), the total minimal sample size increased to 106 patients.

Randomization

A web-based computerized and central randomization service was used for the allocation of the participants (www.randomizer.at) with prestratification for center. The patients were randomized after admission to the hospital and blinded to the treatment group.

Statistical Analysis

We analyzed all patients in an intent-to-treat manner. To compare the postoperative outcomes between the propofol and sevoflurane group, we used linear regression analysis for continuous outcomes (e.g., transaminases), logistic regression analysis for binary outcomes (e.g., EAD), and ordered logistic regression analysis for ordinal outcomes (Clavien-Dindo complication index²⁰), always with group allocation as independent variable. For continuous outcomes, descriptive results are presented as medians (interquartile range, IQR), and the results from the linear regression analyses are presented as the mean difference (with 95% confidence interval, CI). For binary outcomes, we present the absolute numbers of events (proportion in %) in the first columns and the results from the logistic and ordered logistic regression analyses as odds ratio with 95% CI. We adjusted all analyses using a multivariate analysis for center as well as for age and sex of the recipients (results not shown) due to a slight imbalance between groups with regard to age and sex (Table 1). Transformation of continuous variables was tested, but the assumptions of linear regression (normality and homoscedasticity of residuals) were met similarly, as

TABLE 1.
Baseline characteristics of donors and recipients

	Propofol	Sevoflurane
Donors	48	50
Age: median (IQR), y	55 (38-65)	48 (41-59)
Sex: male (%)	25 (52)	29 (59)
AST: median (IQR), U/L	58.5 (26-162.5)	56.5 (27.5-134)
ALT: median (IQR), U/L	41.5 (24-125.5)	46.5 (17.5-85)
Bilirubin: median (IQR), $\mu\text{mol/L}$	5.6 (0.5-11.5)	9.0 (2.7-10.9)
Liver weight: median (IQR), g	1440 (1253-1769)	1497 (1292-1782)
Macrosteatosis $\geq 30\%$: number (%)	2 (4)	3 (6)
CVA as cause of brain death: number (%)	23 (49)	23 (47)
Recipients	48	50
Age: median (IQR), y	53 (37-61)	58 (51-64)
Sex: male (%)	41 (85)	33 (66)
ASA: median (IQR)	III (III-IV)	III (III-IV)
MELD: median (IQR)	19 (11-24)	17 (10-27)
Primary indication for TPL, number (%)		
ESLD (cirrhosis)	29 (60%)	25 (48%)
Tumor (HCC)	10 (21%)	14 (28%)
Other	9 (19%)	12 (24%)
Baseline AST: median (IQR), U/L	60 (42-94)	64 (37-134)
Baseline ALT: median (IQR), U/L	41 (28-72)	49 (25-89)
Bilirubin: median (IQR), $\mu\text{mol/L}$	43 (16-87)	40 (14-110)
APh: median (IQR), U/L	129 (96-224)	120 (86-171)
Quick: % (IQR)	60 (41-78)	54 (40-77)
Liver weight mismatch: % (IQR)	0.98 (0.76-1.18)	1.05 (0.79-1.20)

Mismatch: expected liver weight calculated using the formula of Urata et al.²² and Lemke et al.²³ ASA, American Society of Anesthesiologists; APh, alkaline phosphatase; CVA, cerebrovascular accident; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; TPL, transplantation.

compared to the analyses with untransformed variables, and the results remained essentially the same. To compare transaminases between groups, from baseline measurements (pre-operative day) to 7 postoperative days, a random effects model was used that took the correlated structure of repeated measurements into consideration (xtreg command of STATA). Interquartile range was 25 to 75 percentile. *P* values, 2-tailed, less than 0.05 were defined as statistically significant. All analyses were conducted using STATA (STATA for Windows, version 10.2, Stata Corp; College Station, TX).

RESULTS

Patients

Figure 1 illustrates in detail the patient flow from the screening of potential participants to the final assessment. During the study period, 343 patients were assessed for eligibility, 112 were randomized with 72 in Zurich, 26 in Sao Paulo, and 14 in Ghent. Fourteen patients dropped out because they did not receive a transplant after randomization on admission. Ninety-eight patients were finally included in the study, 50 in the sevoflurane and 48 in the control (propofol) group (66 in Zurich, 22 in Sao Paulo and 10 in Ghent).

Decisions to change the allocated procedure were based on the anesthesiologists concerns for the safety of the patient. One patient in the propofol group crossed to volatile anesthesia, and one patient of the propofol group received sevoflurane due to cardiovascular instability during anesthesia. Sevoflurane was additionally applied to another patient in the propofol group due to insufficient hypnosis with propofol as single anesthetic. Patients' data were analyzed in the original group to which they were randomly assigned (intent to treat).

Baseline characteristics of the 2 study groups were well matched, as presented in Table 1. Donor characteristics were similar with regard to age, sex, AST, ALT, bilirubin, and liver

weight. Macrosteatosis 30% or higher was found in only 5 grafts (2 in the propofol and 3 in the sevoflurane group). Most livers were procured from donors after brain death, 2 livers from donors after cardiac death (1 in each group). Cerebrovascular accident was the most frequent reason for brain death donors with 23 (49%) in the propofol and 23 (47%) in the sevoflurane group.

With regard to recipient characteristics, no difference between groups was observed for the American Society of Anesthesiologists physical status classification, laboratory MELD score, indications for transplantation (hepatitis C and retransplantation included), as well as baseline values of hepatic biochemical markers. Also, transplanted liver volume in relation to recipient's body weight was comparable in both groups. There was a slight difference in age with a median of 53 years (IQR, 37-61 years) in the propofol and 58 years (IQR, 51-64 years) in the sevoflurane arm, as well as sex with 41 (85%) men in the propofol and 33 (66%) in the sevoflurane group.

We adjusted all analyses using a multivariate analysis for center as well as for age and sex of the recipients due to a slight imbalance between groups with regard to age and sex (Table 1).

Intraoperative Data

The median cold ischemia time was comparable in both groups (414 minutes, IQR, 350-585 minutes in the propofol and 455 minutes, IQR, 352-553 minutes in the sevoflurane group) (Table 2). Also, warm ischemia time was similar in both groups with a median of 54 minutes (IQR, 40-65 min) for propofol, and 54 min (IQR, 42-68 min) for sevoflurane patients. Operating time and transfusion of blood products were comparable. Patient's hemodynamic was controlled based on institutional protocols aiming at an optimal perfusion of the organs. No "significant" reperfusion syndrome was described.

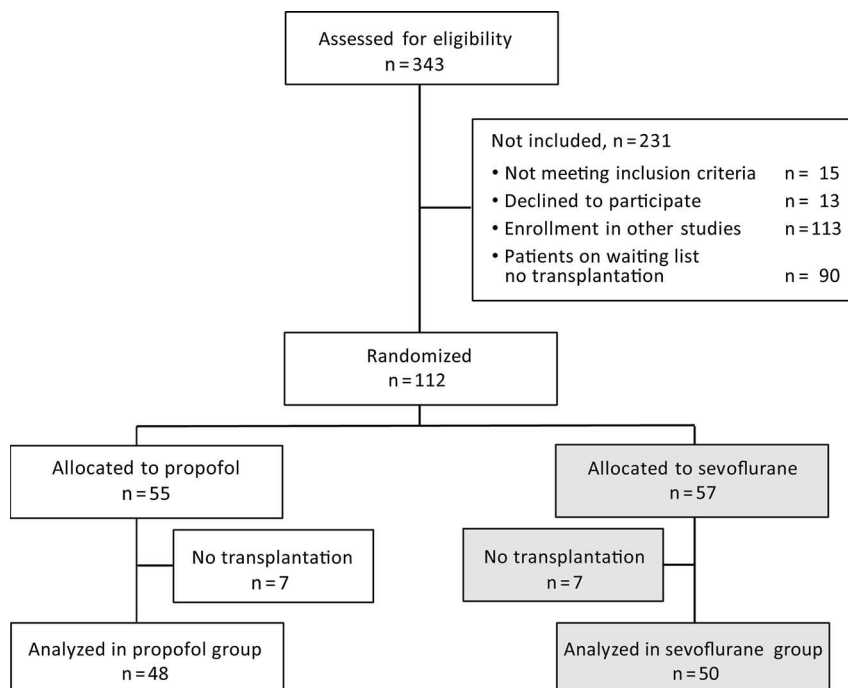


FIGURE 1. Enrollment and randomization of patients.

TABLE 2.**Intraoperative parameters for the propofol and sevoflurane group**

	Propofol (n = 48)	Sevoflurane (n = 50)
Cold ischemia time: median (IQR), min	414 (350-585)	455 (352-553)
Warm ischemia time: median (IQR), min	54 (40-65)	54 (42-68)
Red blood cells received: n (%) ^a	26 (70)	25 (64)
median (IQR) if received	4 (2-8)	6 (2-10)
Frozen plasma received: n (%) ^a	9 (24)	8 (21)
median (IQR) if received	4 (4-8)	10 (7-27)
Platelets received: n (%) ^a	16 (43)	15 (39)
median (IQR) if received	2 (1-2)	1 (1-4)

^a Data missing for 22 patients.**Biochemical Endpoints**

The primary endpoint of the study, the median postoperative peak value of AST, was similar in both groups with a median of 925 U/L (IQR, 512-3274 U/L) and 1097 U/L (IQR, 540-2633 U/L) in the propofol and the sevoflurane group, respectively, with an adjusted mean difference of 215 U/L (95% CI, -1017 to 1448 U/L, $P = 0.73$) (Table 3). Without adjustment for age and sex, the results were a mean difference of 196 U/L (95% CI, -964 to 1356 U/L; $P = 0.74$).

The secondary endpoint, median peak value of ALT, was similar in both groups with 781 U/L (IQR, 405-2063 U/L) in the propofol and 711 U/L (IQR, 424-1645 U/L) in the sevoflurane group. Mean difference was -162 U/L (95% CI, -722 to 399 U/L; $P = 0.57$) (without adjustment for age and sex: -114 U/L (95% CI, -640 to 411 U/L, $P = 0.67$)). The lack of difference between groups was also supported by evaluating repeated AST and ALT measurements starting at the 1st and ending at the 7th postoperative day. For AST, the mean difference between the 2 groups over 7 days was 49 U/L (95% CI, -348 to 445 U/L; $P = 0.81$), for ALT 4 U/L (95% CI, -256 to 263 U/L; $P = 0.98$). Considering the fact that the size of the transplanted liver might have had impact on the release of transaminases, AST values were recalculated in correlation to the liver weight. Also, these results showed no significant difference between both groups (Table 3).

No difference between groups with regard to other postoperatively determined biochemical markers, such as bilirubin, alkaline phosphatase, and Quick, were observed (Table 3).

TABLE 3.**Comparison of postoperative biochemical outcomes for propofol and sevoflurane group**

	Propofol	Sevoflurane	Mean difference (95% CI), P^a
Peak AST: median (IQR), U/L	925 (512-3274)	1097 (540-2633)	215 (-1017 to 1448), 0.73
Peak ALT: median (IQR), U/L	781 (405-2063)	711 (424-1645)	-162 (-722 to 399), 0.57
Peak AST (in relation to g liver weight): median (IQR), U/L · g	0.76 (0.43-1.99)	0.69 (0.41-1.76)	0.14 (-0.58-0.86), 0.70
AST: repeated measurements from days 1 to 7, U/L			49 ^b (-348 to 445), 0.81
ALT: repeated measurements from days 1 to 7, U/L			4 ^b (-256 to 263), 0.98
AST (in relation to g liver weight): Repeated measurements from days 1 to 7, U/L · g			0.03 (-0.28-0.35), 0.84
Bilirubin: repeated measurements from days 1 to 7, μmol/L			3 ^b (-23 to 30), 0.81
Aph: repeated measurements from days 1 to 7, U/L			18 ^b (-18 to 54), 0.33
Quick: repeated measurements from days 1 to 7, %			-2 ^b (-7 to 4), 0.50

^a All comparisons are adjusted for center and age and sex of recipient.^b Difference is mean difference between groups over days 1 to 7.

Early allograft dysfunction as defined at day 7 occurred in 7 patients (14%) in the sevoflurane group compared to 11 (23%) in the propofol group (odds ratio, 0.64; 95% CI, 0.20 to 2.02, $P = 0.45$) (Table 4).

Clinical Outcome

Hospital mortality was 4 of 48 patients (8.3%) in the propofol and 2 of 50 patients (4.0%) in the sevoflurane group. Overall morbidity rate was not significantly different between the groups (odds ratio, 0.66; 95% CI, 0.24 to 1.81, $P = 0.42$) (Table 4). Major complications (grade IIIb-V) were not different between groups (50% vs 40% for propofol vs the sevoflurane group (odds ratio, 0.58; 95% CI, 0.24 to 1.41; $P = 0.23$)). Severity of complications between groups showed an effect in favor of the sevoflurane group, but were not significantly different with a median of grade II complications (IQR, 0-IIIb) in the sevoflurane compared to median of grade IIIa (IQR, II-IVb) in the propofol group (odds ratio, 0.51; 95% CI, 0.24 to 1.09; $P = 0.08$). Clinically relevant outcome variables, such as ICU stay (median of 4 days in both groups with a mean difference of -1 day, 95% CI, -4 to 2 days, $P = 0.64$), as well as length of hospital stay (median of 18 days in the sevoflurane compared to 21 days in the propofol group, mean difference of -1 day; 95% CI, -8 to 6 days; $P = 0.77$) were not significantly different.

DISCUSSION

This is the first multicenter RCT, which evaluates whether application of sevoflurane in patients undergoing liver transplantation reduces postoperative ischemia-reperfusion injury and has an impact on clinical outcome. In our trial setting, sevoflurane has no benefit over a propofol-based regimen in liver transplantation.

Testing of variants of clinical management in transplant anesthesia in the form of randomized clinical trials has been rare and we therefore consider it important to report our negative finding in a trial that has been performed using "state-of-the-art" methodology.

The main limitation of this trial is the choice of a surrogate marker as the primary endpoint instead of a clinical outcome parameter. Although the release of liver enzymes are accepted biochemical markers for acute organ injury after transplantation and has been used in many other RCTs,²⁸ they represent markers of unknown significance for the clinician. Clinical outcome should therefore be preferred as

TABLE 4.
Comparison of postoperative clinical outcomes for the propofol and sevoflurane group

	Propofol	Sevoflurane	Odds ratio (95% CI), <i>P</i> ^a
In hospital mortality: n (%)	4 (8.3)	2 (4.0)	—
Any complication: n (%)	38 (79)	37 (74)	0.66 ^b (0.24 to 1.81), 0.42
Highest complication: median (IQR)	Grade IIIa (II-IVb)	Grade II (0-IIIb)	0.51 ^c (0.24 to 1.09), 0.08
Major complication (IIIb-V): n (%)	24 (50)	20 (40)	0.58 ^d (0.24 to 1.41), 0.23
EAD ^e at day 7: n (%)	11 (23)	7 (14)	0.64 ^f (0.20 to 2.02), 0.45
ICU stay: median (IQR), d	4 (2-6)	4 (3-9)	—1 (−4 to 2), 0.64
Length of hospital stay: median (IQR), d	21 (11-25)	18 (12-33)	−1 (−8 to 6), 0.77

^a All comparisons are adjusted for center and age and sex of recipient.

^b Odds ratio for any complication.

^c Odds ratio for having a higher grade of complication.

^d Odds ratio for major complication.

^e Early allograft dysfunction (EAD) was defined at day 7 as either Quick \leq 41% or ALT $>$ 2000 U/l or bilirubin \geq 171 μ mol/l based on Guarrera et al. and Stockmann et al. (Ref. 31 and 32, respectively).

^f Odds ratio for early allograft dysfunction (EAD).

primary endpoint for trials,²⁹ but there remains the limitation that an appropriate sample size can rarely be obtained even in multicenter collaboration without extending the time frame beyond practicability. We decided to evaluate a frequently used marker like AST to achieve closure of the trial within a reasonable time frame. Using complications as primary outcome and assuming, based on this trial, that 50% of patients with propofol will have a complication of at least grade IIIa, 408 patients per group would be needed to show a 20% relative reduction with a volatile anesthetic with 80% power or 183 patients per group for a 30% relative reduction, respectively. Enrollment of up to 400 patients to test our hypothesis would not have been possible.

In this context, it is important to point out that an effect on clinical outcomes could be observed in the sevoflurane group that was not significant because the study was not powered to prove or disprove differences in secondary endpoints. In the sevoflurane group, hospital mortality (4.0% *vs* 8.3%) as well as major complication rates (grade IIIb and higher: 40% *vs* 50%) were decreased in comparison to the propofol group. Also, EAD was lower in the sevoflurane group (14% *vs* 23%). A study could certainly be powered in the future to prove or disprove an effect by significance, but it remains questionable if the observed effect size is large enough to justify further investigations along these lines.

Strategies to reduce ischemia-reperfusion injury in transplantation are of high interest because grafts are exposed to a chain of injuries inducing ischemia starting from the initial injury to the donor, over management of donors in ICU settings to the procurement surgery and anesthesia, the transport interval and condition, and finally the recipient surgery. Various anesthetic regimens are nowadays used in liver transplant recipients typically consisting either the use of a modern volatile anesthetic, such as isoflurane, sevoflurane, or desflurane, or the application of the intravenous anesthetic propofol or both. However, there is no higher level evidence on what the best anesthetic agent in liver transplant recipients is with respect to acute graft injury.³⁰

Several previous trials have suggested that volatile anesthetics are organ protective in scenarios of organ ischemia and reperfusion and might improve outcomes after cardiac surgery.³¹ Interestingly, similar trials with volatile anesthetics have also been performed in liver resection surgery where temporary clamping of the liver remnant may evoke ischemic liver injury. Although some studies clearly showed

a benefit of volatile anesthetics,^{10,11,13} others did not.³² We therefore designed an RCT to test the effect of volatile anesthetics in liver transplantation, a situation of ischemia-reperfusion. However, our hypothesis that the transplanted liver endures less acute injury by sevoflurane postconditioning could not be confirmed.

There are at least 2 possible explanations for this observation. The first explanation suggests that our regimen did not have an effect because it was not properly applied. A recently published study showed that preconditioning with volatile anesthetics in the donor has a positive impact on outcomes.³³ In our study, the transplanted graft was not exposed to volatile anesthetics before cross-clamping in the donor because the logistic effort to consent recipients of multiple organs to a randomized anesthetic regimen in donors was felt to be unsurmountable by our teams. Hence, it was not possible to perform preconditioning of graft in this study.

The second explanation is supported by the fact that organ injury in transplantation is caused by a broad variety of factors from organ procurement to preservation and graft implantation. These include donor factors (e.g., age, race, cause of death, summarized as donor risk index³⁴), recipient-specific factors (e.g., co-morbidities, severity of liver disease, reflected in the MELD score²¹), and not at least procedure-related, time (duration of ischemia) as well as immunological factors which might cause graft injury. An effect by a subtle intervention impacting positively on ischemia-reperfusion might be lost in the noise of multiple lines of severe injury to the graft and several hours of warm and cold ischemia. This latter conclusion could explain the nonsignificant effects we observed in favor of the sevoflurane group.

In conclusion, this first multicenter RCT evaluating a volatile anesthetic in liver transplantation recipients failed to show protection from acute organ injury in liver transplantation. Less severe complications and EAD were found in recipients with sevoflurane anesthesia, which suggests an effect that cannot be established beyond doubt in this trial, but might warrant further investigation.

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